EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EAGLE PHARMACEUTICALS, INC. and EAGLE SUB1 LLC Plaintiffs, v. SLAYBACK PHARMA LLC and AZURITY PHARMACEUTICALS, INC., Defendants.	C.A. No. 25-75-JLH **JURY TRIAL DEMANDED**

SECOND AMENDED COMPLAINT

Plaintiffs Eagle Pharmaceuticals, Inc. and Eagle Sub1 LLC (collectively "Eagle"), by its attorneys, for its Second Amended Complaint, alleges as follows:

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, to enjoin, and obtain damages resulting from, Slayback Pharma LLC ("Slayback") and Azurity Pharmaceuticals, Inc.'s ("Azurity") (collectively, "Defendants") unauthorized importation into the United States, and use, sale, and/or offer for sale of products in the United States, that infringe at least one claim of Eagle's United States Patent No. 12,138,248 (the "'248 patent" or the "Patent-in-Suit").

2. Slayback submitted New Drug Application ("NDA") No. 212209 to the United States Food and Drug Administration ("FDA"), seeking approval to manufacture and sell a product that relies on data from bioavailability and/or bioequivalence studies contained in the Approved Labeling for Eagle's BELRAPZO®, 100 mg/4 mL (25 mg/mL) Bendamustine Hydrochloride Injection product, prior to the expiration of the Patent-in-Suit.

3. On information and belief, the FDA granted approval of NDA No. 212209 on December 7, 2022. Following said approval, Slayback began to import into the United States, and/or use, sell, and/or offer to sell in the United States, its NDA Product, VIVIMUSTA® (bendamustine hydrochloride injection) 100 mg/4 mL (25 mg/mL) (the "Azurity NDA Product"), along with the Approved Labeling for the same.

4. On information and belief, Slayback was acquired by Azurity after the filing of the Complaint in *Eagle Pharms., Inc. v. Slayback Pharma LLC*, C.A. No. 24-65-JLH, D.I. 1 (D. Del. Jan. 17, 2024).

5. On information and belief, at some time after the filing of the Complaint in *Eagle Pharms., Inc. v. Slayback Pharma LLC*, C.A. No. 24-65-JLH, D.I. 1 (D. Del. Jan. 17, 2024), Azurity became the NDA holder for NDA No. 212209.

6. On information and belief, Azurity is the current NDA holder for NDA No. 212209. *See* https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=212209#42297 (last visited June 6, 2025).

7. On information and belief, Azurity continues to import into the United States, and/or use, sell, and/or offer to sell in the United States, the Azurity NDA Product, VIVIMUSTA® (bendamustine hydrochloride injection) 100 mg/4 mL (25 mg/mL), along with the Approved Labeling for the same.

PARTIES

8. Plaintiff Eagle Pharmaceuticals, Inc. is a corporation organized and existing under the laws of Delaware, with its corporate offices and principal place of business at 50 Tice Boulevard, Suite 315, Woodcliff Lake, New Jersey 07677.

9. Plaintiff Eagle Sub1 LLC is a limited liability company organized and existing under the laws of Delaware, with its corporate offices and principal place of business at 50 Tice Boulevard, Suite 315, Woodcliff Lake, New Jersey 07677. Eagle Sub1 LLC is a wholly owned subsidiary of Eagle Pharmaceuticals, Inc.

10. On information and belief, Defendant Slayback is a company organized and existing under the laws of Delaware, with its principal place of business at 301 Carnegie Center, #303, Princeton, New Jersey 08540.

11. On information and belief, Slayback is a wholly-owned subsidiary of Azurity.

12. On information and belief, Defendant Azurity is a company organized and existing under the laws of Delaware, with its principal place of business at 8 Cabot Road, Suite 2000 Woburn, MA 01801.

13. On information and belief, Azurity is a generic pharmaceutical company that develops and manufactures generic versions of branded pharmaceutical products that it markets and distributes throughout the United States in concert with its subsidiary, Slayback.

14. On information and belief, Slayback and Azurity act in concert to import the Azurity NDA Product into the United States for sale, offer for sale, and use.

15. On information and belief, Slayback and Azurity are agents of each other, and/or operate in concert as integrated part of the same business group, and enter into agreements with each other that are nearer than arm's length, including with respect to the development, regulatory approval, marketing, sale, offer for sale, and distribution of pharmaceutical products throughout the United States, including in Delaware, and including with respect to the Azurity NDA Product.

16. The Approved Labeling for VIVIMUSTA® recites that it is "Manufactured at: Latina Pharma S.p.A. 04013 Sermoneta (LT), Italy" and "Manufactured for: Slayback Pharma

LLC Princeton, NJ 08540." Approved Labeling for VIVIMUSTA®, (the "Approved Labeling"), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212209s005lbl.pdf (last visited June 6, 2025) at 22. On information and belief, Slayback directly or indirectly markets, sells, and distributes VIVIMUSTA® throughout the United States, including in Delaware.

17. On information and belief, following FDA approval of NDA No. 212209 and the acquisition of Slayback by Azurity, Slayback and Azurity acted and continue to act, in concert to market, distribute, offer for sale, and sell the Azurity NDA Product throughout the United States and within Delaware.

JURISDICTION AND VENUE

18. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

19. Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b), at least because Slayback and Azurity are incorporated in Delaware and therefore reside there for purposes of venue.

20. Based on the facts and causes alleged herein, and for additional reasons to be further developed through discovery if necessary, this Court has personal jurisdiction over Slayback and Azurity.

21. This Court has personal jurisdiction over Slayback because, on information and belief, Slayback is a company organized and existing under the laws of Delaware and maintains a registered agent for service of process in Delaware, at 1209 Orange Street, Wilmington, Delaware, 19801. This Court has personal jurisdiction over Slayback for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

22. This Court has personal jurisdiction over Azurity because, on information and belief, Azurity is a company organized and existing under the laws of Delaware and maintains a registered agent for service of process in Delaware, at 1209 Orange Street, Wilmington, Delaware, 19801. This Court has personal jurisdiction over Azurity for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

23. In addition, this Court has personal jurisdiction over Slayback and Azurity because, on information and belief, Slayback and Azurity have engaged in a persistent course of conduct within Delaware by continuously and systematically placing goods into the stream of commerce for distribution throughout the United States, including Delaware.

24. Further, this Court also has personal jurisdiction over Slayback and Azurity because, among other things, on information and belief: (1) Slayback filed NDA No. 212209 for the purpose of seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of the product described in NDA No. 212209 in the United States, including in Delaware; (2) Azurity acquired Slayback and became the NDA Holder for NDA No. 212209; and (3) since NDA No. 212209 was approved, the product described in NDA No. 212209, VIVIMUSTA®, has been and continues to be imported, marketed, distributed, offered for sale, and/or sold in the United States, including in Delaware.

25. The Court also has personal jurisdiction over Slayback and Azurity because they have committed, aided, abetted, induced, contributed to, or participated in the commission of the tortious act of patent infringement that has harmed and injured Eagle, which is a Delaware corporation.

26. Slayback has previously consented to jurisdiction in Delaware in many prior cases arising out of the filing of its drug applications, including the application for the product at issue

in this litigation, and it has asserted counterclaims in such cases. *See, e.g., Cephalon, Inc. & Eagle Pharm., Inc. v. Slayback Pharma LLC*, No. 17-1154-CFC, D.I. 11 (D. Del. Sep. 29, 2017); *Teva Pharma. Int'l GmbH, Cephalon, Inc. & Eagle Pharma., Inc. v. Slayback Pharma LLC*, No. 18-117-CFC, D.I. 9 (D. Del. Feb. 12, 2018); *Eagle Pharm., Inc. v. Slayback Pharma LLC*, No. 18-1459-CFC, D.I. 9 (D. Del. Oct. 10, 2018); *Eagle Pharm., Inc. v. Slayback Pharma LLC*, No. 18-1953-CFC, D.I. 12 (D. Del. Jan. 3, 2019); *Eagle Pharm. Inc. v. Slayback Pharma LLC*, No. 21-1256-CFC, D.I. 9 (D. Del. Sept. 22, 2021); *Eagle Pharm., Inc. v. Slayback Pharma LLC*, No. 24-65-JLH, D.I. 14 (D. Del. Apr. 1, 2024).

27. Azurity has previously consented to jurisdiction in Delaware in many prior cases, arising out of its manufacture, use, offer for sale, sale and/or importation of pharmaceutical products, including cases that it initiated as plaintiff. *See, e.g., Azurity Pharms., Inc. v. Hetero Lab'ys Ltd.*, C.A. No. 24-396-MN, D.I. 1 (D. Del. Mar. 28, 2024); *Azurity Pharms., Inc. v. Zydus Pharms (USA) Inc.*, C.A. No. 23-833-MN, D.I. 1 (D. Del. Aug. 2, 2023); *Azurity Pharms., Inc. v. Teva Pharms., Inc.*, C.A. No. 23-1080-MN, D.I. 1 (D. Del. Sept. 29, 2023); *Azurity Pharms., Inc. v. Accord Healthcare, Inc.*, C.A. No. 23-373-CFC, D.I. 1 (D. Del. Mar. 31, 2023); *Azurity Pharms., Inc. v. Novitium Pharma, LLC*, C.A. No. 23-163-MSG, D.I. 1 (D. Del. Feb. 14, 2023); *Azurity Pharms., Inc. v. Glenmark Pharms., Inc.*, C.A. No. 22-1604-MN, D.I. 1 (D. Del. Dec. 16, 2022); *Azurity Pharms., Inc. v. Aurobindo Pharma Ltd.*, C.A. No. 21-1707-MSG, D.I. 1 (D. Del. Dec. 2, 2021); *Azurity Pharms., Inc. v. CoreRx, Inc.*, C.A. No. 21-1522-LPS, D.I. 1 (D. Del. Oct. 27, 2021); *Azurity Pharms., Inc. v. Bionpharma Inc.*, C.A. No. 21-1455-MSG, D.I. 1 (D. Del. Oct. 15, 2021); *Heron Therapeutics, Inc. v. Azurity Pharms., Inc.*, C.A. No. 24-1363-WCB, D.I. 22 (D. Del. Jan. 10, 2025).

28. For at least the above reasons, it would not be unfair or unreasonable for Slayback and Azurity to litigate this action in this District, and there is personal jurisdiction over Slayback and Azurity for purposes of this action.

BACKGROUND

29. BELRAPZO®, which contains bendamustine hydrochloride, is an alkylating drug that is indicated for the treatment of patients with chronic lymphocytic leukemia, as well as for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

30. Eagle Pharmaceuticals, Inc. is the holder of NDA No. 205580 for BELRAPZO®, which has been approved by the FDA.

31. The ’248 patent, entitled “Formulations of Bendamustine” (Exhibit A hereto), was duly and legally issued on November 12, 2024. Eagle Sub1 LLC is the owner and assignee of the ’248 patent. Eagle Pharmaceuticals, Inc. has an exclusive license to the ’248 patent to develop, manufacture, use, offer to sell, sell, promote, distribute, export and import, enforce, and otherwise exploit the ’248 patent with respect to BELRAPZO®.

32. Eagle Pharmaceuticals, Inc. timely submitted the ’248 patent to be listed in connection with BELRAPZO® in the FDA’s publication *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the “Orange Book.”

33. Claim 1 of the ’248 patent recites:

> A sterile container containing a liquid bendamustine-containing composition comprising
>
> bendamustine, or a pharmaceutically acceptable salt thereof, wherein the bendamustine concentration in the composition is about 25 mg/mL;
>
> a pharmaceutically acceptable fluid consisting of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol; and
>
> a stabilizing amount of an antioxidant,

wherein the total impurities resulting from the degradation of the bendamustine is less than about 5% peak area response, as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of about 5 °C to about 25 °C.

34. BELRAPZO® is a product that falls within the ambit of at least claim 1 of the '248 patent.

35. The '248 patent is also listed in the Orange Book for BENDEKA®. BENDEKA® likewise is a drug product that falls within the ambit of at least claim 1 of the '248 patent.

INFRINGEMENT BY DEFENDANTS

36. On information and belief, the Azurity NDA Product, marketed and sold as VIVIMUSTA®, received final approval from the FDA on December 7, 2022. *See* Drugs@FDA, Vivimusta, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212209 (last visited June 6, 2025).

37. On information and belief, since the approval of VIVIMUSTA®, Defendants have been importing VIVIMUSTA® into the United States, using VIVIMUSTA® in the United States, offering VIVIMUSTA® for sale in the United States, and selling VIVIMUSTA® in the United States. VIVIMUSTA® is prominently listed as a product for sale by Defendants on their website. *See* https://vivimusta.com (last visited June 6, 2025).

38. On information and belief, since Azurity acquired Slayback and became the NDA holder for NDA No. 212209, Azurity has become responsible for advertising, marketing, promoting, offering for sale, selling and/or importing the Azurity NDA Product, VIVIMUSTA®, in the United States. *See* https://azurity.com/azurity-pharmaceuticals-acquires-slayback-pharma (last visited June 6, 2025).

39. Azurity's websites include promotional materials directed to the marketing, promotion, and sale of the Azurity NDA Product, VIVIMUSTA®, including the Approved

Labeling. *See, e.g.*, https://azurity.com/products (last visited June 6, 2025); https://vivimusta.azuritysolutions.com (last visited June 6, 2025); https://www.vivimustaconnect.com (last visited June 6, 2025); https://azurity.com/wp-content/uploads/2023/11/VIVIMUSTA_PI.pdf (last visited June 6, 2025); https://www.vivimustaconnect.com/doctor_cases/new (last visited June 6, 2025).

40. On information and belief, VIVIMUSTA® relies on data from bioavailability and/or bioequivalence studies contained in the Approved Labeling for BELRAPZO®. BELRAPZO® is approved for a 24-month shelf life. The Approved Labeling for VIVIMUSTA® does not identify any difference in stability between VIVIMUSTA® and BELRAPZO® and, on information and belief, VIVIMUSTA® has the same or substantially similar stability as BELRAPZO® and/or as recited in the claims of the Patent-in-Suit.

41. Publicly-available materials from the FDA's review of Azurity's NDA No. 212209 indicate that "in the September 16, 2019 CRL, [Slayback] provided updated stability data for the finished product in support of the proposed 24-month expiry. Based on the information provided, Slayback Pharma LLC. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at [sic] between 2–8 °C." Product Quality Review(s), Application No. 212209Orig1s000, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/212209Orig1s000ChemR.pdf (last visited June 6, 2025) (the "Product Quality Review") at p. 37. Thus, on information and belief, VIVIMUSTA®, as sold, used, or offered for sale in the United States, satisfies the stability limitations set forth in the claims of the Patent-in-Suit.

42. The Approved Labeling for VIVIMUSTA® states that the active ingredient is bendamustine hydrochloride. *See* Approved Labeling at 1; *see also Eagle Pharm., Inc. v. Slayback Pharma LLC*, 958 F.3d 1171, 1173 (Fed. Cir. 2020).

43. The Approved Labeling for VIVIMUSTA® states that the dosage strength is 25 mg/mL. *See id.*

44. The Approved Labeling for VIVIMUSTA® states that it contains polyethylene glycol ("PEG"), which is described and claimed as a pharmaceutically acceptable fluid in the Patent-in-Suit. *See id.* at 15. The Approved Labeling for VIVIMUSTA® further states that it contains "absolute alcohol," which is a known, commercially available grade of ethanol, which is likewise described and claimed as a pharmaceutically acceptable fluid in the Patent-in-Suit. *See id.* Thus, Defendants' VIVIMUSTA® contains "a pharmaceutically acceptable fluid consisting of polyethylene glycol and optionally . . . ethanol," consistent with claim 1 of each of the Patent-in-Suit.

45. The Approved Labeling for VIVIMUSTA® also recites that "[e]ach milliliter contains 25 mg of bendamustine hydrochloride equivalent to 22.7 mg of bendamustine, 5 mg of monothioglycerol, 39.45 mg (5% v/v) of absolute alcohol, and q.s. to 1 mL polyethylene glycol 400." *Id.* at 15. The Approved Labeling then states: "Sodium hydroxide is used to adjust [the] pH of polyethylene glycol 400." *Id.* Sodium hydroxide is not a pharmaceutically acceptable fluid as that term is used in the specification of the '248 patent, nor is it a component of the pharmaceutically acceptable fluid in VIVIMUSTA®. Thus, it is not pertinent to the "pharmaceutically acceptable fluid" limitation of claim 1 of each of the Patent-in-Suit.

46. Indeed, in referring to the use of sodium hydroxide, the Approved Labeling does not describe sodium hydroxide as a component of VIVIMUSTA®, but rather notes that "sodium hydroxide is used to adjust [the] pH ***of polyethylene glycol 400***" used to manufacture VIVIMUSTA®. *Id.* at 15. Thus, that fluid remains "***polyethylene glycol 400***" and is not taken

outside the confines of being a "pharmaceutically acceptable fluid" by any use of sodium hydroxide during its preparation.

47. The Approved Labeling notes that VIVIMUSTA® is "Manufactured at: Latina Pharma S.p.A." in "Sermoneta (LT), Italy." *Id.* at 22. In certain instances, on information and belief, Defendants' Italian manufacturer uses sodium hydroxide in batches of PEG. In those instances, any addition of sodium hydroxide to the PEG during manufacturing in Italy is for the purposes of ensuring that VIVIMUSTA® has a pharmaceutically acceptable fluid as part of its liquid bendamustine-containing formulation at the time of importation, offer for sale, use, and/or sale of same in the United States.

48. Publicly-available materials from the FDA's review of Azurity's NDA No. 212209 indicate that sodium hydroxide is only used in a "quantity sufficient" to "adjust [the] pH of polyethylene glycol 400." Product Quality Review at p. 6, 67.

49. The Approved Labeling similarly does not list a specific amount of sodium hydroxide or indicate that it is necessary in all instances. Rather, the Approved Labeling for VIVIMUSTA® recites that "[e]ach milliliter contains 25 mg of bendamustine hydrochloride equivalent to 22.7 mg of bendamustine, 5 mg of monothioglycerol, 39.45 mg (5% v/v) of absolute alcohol, and q.s. to 1 mL polyethylene glycol 400." *Id.* at 15. Therefore, on information and belief, while the Approved Labeling states that "[s]odium hydroxide is used to adjust [the] pH of polyethylene glycol 400" in VIVIMUSTA® (Approved Labeling at 15), sodium hydroxide is not used for each batch of the PEG used in the manufacture of VIVIMUSTA®.

50. Even in an instance where sodium hydroxide is used to adjust the pH of batches of PEG used to manufacture VIVIMUSTA®, on information and belief, sodium hydroxide is not a component of the product that is imported into the United States, sold and/or offered for sale in

the United States, and/or used in the United States. Thus, the Approved Labeling for VIVIMUSTA® recites that "[e]ach milliliter contains 25 mg of bendamustine hydrochloride equivalent to 22.7 mg of bendamustine, 5 mg of monothioglycerol, 39.45 mg (5% v/v) of absolute alcohol, and q.s. to 1 mL polyethylene glycol 400." *Id.* at 15. As explained on Defendants' Approved Labeling, sodium hydroxide is used as a pH adjuster and, on information and belief, is consumed by such use and/or is otherwise not a component of VIVIMUSTA®.

51. Additionally, the use of sodium hydroxide is well known to those of skill in the art to adjust the pH of both pharmaceutical formulations generally, and of PEG specifically. Sodium Hydroxide, National Library of Medicine, https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-Hydroxide, (last visited June 6, 2025). Thus, even if Defendants' Italian manufacturer uses sodium hydroxide to adjust the pH of PEG in the manufacturing process, a person of ordinary skill in the art would not consider any such use to take VIVIMUSTA® outside the scope of the claim element "a pharmaceutically acceptable fluid consisting of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol." *See, e.g.*, '248 patent at claim 1. Further, by time of importation, offer for sale, use, and/or sale, VIVIMUSTA® has a pharmaceutically acceptable fluid as part of its liquid bendamustine-containing formulation given that Defendants promote that it is pharmaceutically acceptable for administration to humans. "VIVIMUSTA is an alkylating drug indicated for the treatment of adult patients . . ." https://vivimusta.com/ (last visited June 6, 2025).

52. The Approved Labeling for VIVIMUSTA® also recites that "[e]ach milliliter contains 25 mg of bendamustine hydrochloride [and] . . . 5 mg of monothioglycerol." Approved Labeling at 15. The shared specification for the Patent-in-Suit indicates that monothioglycerol is an antioxidant and that 5 mg/mL is a stabilizing amount of an antioxidant.

53. On information and belief, VIVIMUSTA® has less than about 5% peak area response of total impurities resulting from the degradation of the bendamustine, as determined by HPLC at a wavelength of 223 nm after at least 15 months at a temperature of from about 5 °C to about 25 °C. Further, Defendants have conceded that VIVIMUSTA® meets an identical limitation in U.S. Patent No. 9,572,796, which is related to the Patent-in-Suit and shares a specification with them. *Eagle Pharmaceuticals Inc. v. Slayback Pharma LLC*, 958 F.3d 1171, 1173 (Fed. Cir. 2020).

54. The Approved Labeling for VIVIMUSTA® encourages, recommends, instructs, and/or promotes administration to patients with chronic lymphocytic leukemia. *See* Approved Labeling.

COUNT I – INFRINGEMENT OF U.S. PATENT NO. 12,138,248

55. Eagle incorporates each of the preceding paragraphs as if fully set forth herein.

56. As set forth herein, Defendants have offered VIVIMUSTA® for sale in the United States, sold VIVIMUSTA® in the United States, used VIVIMUSTA® in the United States, and/or imported VIVIMUSTA® into the United States.

57. On information and belief, the importation, manufacture, sale, offer for sale, and/or use of VIVIMUSTA® in conjunction with its Approved Labeling infringes one or more claims, including at least claim 1, of the ’248 patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, and/or Defendants induce or contribute to the inducement of the infringement of one or more claims, including at least claim 1, of the ’248 patent under 35 U.S.C. § 271(b) and/or (c).

58. As reflected in its Approved Labeling, each milliliter of VIVIMUSTA® “contains 25 mg of bendamustine hydrochloride equivalent to 22.7 mg of bendamustine, 5 mg of

monothioglycerol, 39.45 mg (5% v/v) absolute alcohol, and q.s. to 1 mL polyethylene glycol 400." Approved Labeling at 15. That Approved Labeling further indicates that VIVIMUSTA® is marketed in a 100 mg/4 mL vial. *Id.* at 20.

59. The foregoing actions by Defendants constitute infringement of the '248 patent, active inducement of infringement of the '248 patent, and contribution to the infringement by others of the '248 patent.

60. Defendants' infringement and/or inducement is willful. On information and belief, Defendants are aware of the '248 patent at least because Slayback is aware of Eagle's patent portfolio and has previously been involved in litigation concerning other patents related to the '248 patent. *See, e.g.*, *Eagle Pharm. Inc. v. Slayback Pharma LLC*, No. 21-1256-CFC, D.I. 9 (D. Del. Sept. 22, 2021). Further, Defendants have been aware of the '248 patent and their related infringement at least since Eagle Pharmaceuticals, Inc. sent a letter to Slayback dated November 12, 2024, informing Slayback that the '248 patent had issued and that the importation, sale, offer for sale, and/or use of VIVIMUSTA® in conjunction with its Approved Labeling infringed the '248 patent. Moreover, on information and belief, Defendants have regularly monitored Eagle's patent filings and developments in the '248 patent family.

61. On information and belief, Defendants have acted with full knowledge of the '248 patent and/or the application leading to the '248 patent, Application No. 18/646,171, and without a reasonable basis for believing that it would not be liable for infringing the '248 patent, actively inducing infringement of the '248 patent, and contributing to the infringement by others of the '248 patent.

62. Unless Defendants are enjoined from infringing the ’248 patent, actively inducing infringement of the ’248 patent, and contributing to the infringement by others of the ’248 patent, Eagle will suffer irreparable injury. Eagle has no adequate remedy at law.

63. Eagle has suffered monetary damages, including but not limited to lost profits, as a result of Defendants’ infringement of the ’248 patent.

JURY DEMAND

64. Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Eagle hereby demands a trial by jury on all issues triable as such.

PRAYER FOR RELIEF

WHEREFORE, Eagle requests the following relief:

(a) A judgment that Defendants have infringed, and induced and contributed to infringement of the Patent-in-Suit;

(b) A permanent injunction pursuant to, *inter alia*, 35 U.S.C. § 283 enjoining Defendants, their officers, agents, servants, employees and attorneys, and all persons acting in concert with them, from making, using, selling, offering for sale, marketing, distributing, or importing the Azurity NDA Product, VIVIMUSTA®, or any product the making, using, offering for sale, sale, marketing, distribution, or importation of which infringes the Patent-in-Suit, or the inducement of or the contribution to any of the foregoing, prior to the expiration date of the Patent-in-Suit, inclusive of any extension(s) and additional period(s) of exclusivity;

(c) A judgment declaring that making, using, selling, offering for sale, marketing, distributing, or importing the Azurity NDA Product, VIVIMUSTA®, or any product or compound the making, using, offering for sale, sale, marketing, distribution, or importation of which infringes the Patent-in-Suit, prior to the expiration date of the Patent-in-Suit, respectively, will infringe,

actively induce infringement of, and/or contribute to the infringement by others of the Patent-in-Suit;

(d) An award of Eagle's damages or other monetary relief to compensate Eagle for Defendants' past infringement and any continuing or future infringement of the Patent-in-Suit up until the date such judgement is entered, including pre- and post-judgement interest, costs, and disbursements as justified pursuant to 35 U.S.C. § 284;

(e) A declaration that this case is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(f) An award of Eagle's costs and expenses in this action; and

(g) Such further and other relief as this Court may deem just and proper.

Dated: June 9, 2025

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EXHIBIT A

US012138248B2

(12) **United States Patent**
Palepu et al.

(10) **Patent No.: US 12,138,248 B2**
(45) **Date of Patent: *Nov. 12, 2024**

(54) **FORMULATIONS OF BENDAMUSTINE**

(71) Applicant: **Eagle Pharmaceuticals, Inc.**, Woodcliff Lake, NJ (US)

(72) Inventors: **Nagesh R. Palepu**, Southampton, PA (US); **Philip Christopher Buxton**, Uxbridge (GB)

(73) Assignee: **Eagle Pharmaceuticals, Inc.**, Woodcliff Lake, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/646,171**

(22) Filed: **Apr. 25, 2024**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(57) **ABSTRACT**

Long term storage stable bendamustine-containing compositions are disclosed. The compositions can include bendamustine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable fluid which can include in some embodiments PEG, PG or mixtures thereof and an antioxidant or chloride ion source. The bendamustine-containing compositions have less than about 5% total impurities, on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

22 Claims, No Drawings

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FORMULATIONS OF BENDAMUSTINE

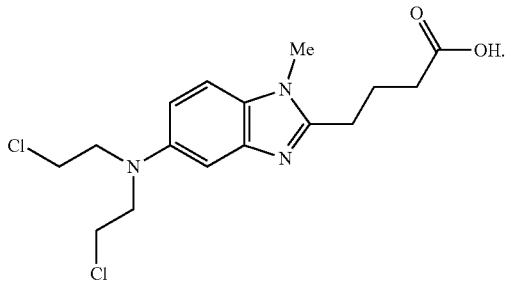
CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 18/498,259, filed Oct. 31, 2023, which is a continuation of application Ser. No. 16/509,920, filed Jul. 12, 2019, now U.S. Pat. No. 11,103,483, which is a continuation of application Ser. No. 16/015,656, filed Jun. 22, 2018, which is a continuation of application Ser. No. 15/432,335, filed Feb. 14, 2017, now U.S. Pat. No. 10,010,533, issued Jul. 3, 2018, which is a continuation of application Ser. No. 15/013,436, filed Feb. 2, 2016, now U.S. Pat. No. 9,572,797, issued Feb. 21, 2017, which is a continuation of application Ser. No. 14/031,879, filed Sep. 19, 2013, now U.S. Pat. No. 9,265,831, issued Feb. 23, 2016, which is a continuation of application Ser. No. 13/016,473, filed Jan. 28, 2011, now U.S. Pat. No. 8,609,707, issued Dec. 17, 2013, which claims the benefit of U.S. Provisional Patent Application No. 61/299,100, filed Jan. 28, 2010, the contents of each of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine free base is represented by the following structural formula (I)

(I)



Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkins disease and multiple myelomas. Bendamustine is the active ingredient of the commercial product Treanda™, a lyophilized powder for reconstitution.

Bendamustine exhibits rapid degradation upon reconstitution of the lyophilized product. Bendamustine undergoes hydrolysis by direct substitution rather than an addition elimination process due to the presence of the highly labile aliphatic chlorine atoms. Some of the main degradants of bendamustine are the monohydroxy compound known as HP1 (hydrolysis product 1) and dihydroxy compound HP2 (hydrolysis product 2). The monohydroxy compound appears as the main impurity at Relative Retention Time (RRT) 0.6 and the dihydroxy compound appears as the main impurity at RRT 0.27. Minor peaks appear at RRT 1.2, which are presently unknown.

The stability of bendamustine in water is measured in hours, and is therefore, not suitable for long-term storage in liquid form. The lyophile possesses good chemical stability. However, reconstitution of the lyophile is clinically inconvenient, taking 15-30 mins with implications of chemical instability. There is a need for ready to use (RTU) bendamustine formulations having enhanced stability.

SUMMARY OF THE INVENTION

In other aspects of the invention, the bendamustine-containing compositions include a) a pharmaceutically acceptable fluid which contains one or more of propylene glycol, ethanol, polyethylene glycol, benzyl alcohol and glycofurol, and b) a stabilizing amount of a chloride salt. In other aspects of the invention, the bendamustine-containing compositions include DMSO (dimethyl sulfoxide) as part of the pharmaceutically acceptable fluid included therein. Regardless of the pharmaceutically acceptable fluid included, the amount of bendamustine included in the composition is preferably from about 20 mg/mL to about 60 mg/mL. Still further aspects of the invention include methods of treatment using bendamustine-containing compositions and kits containing the same.

One of the advantages of the inventive liquid compositions is that they have substantially improved long term stability when compared to currently available formulations. For example, the inventive bendamustine compositions are substantially free of impurities after at least about 15 months at a temperature of from about 5° C. to about 25° C. The inventive formulations are advantageously ready to use or ready for further dilution. Reconstitution of lyophilized powders is not required.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, RRT is calculated by dividing the retention time of the peak of interest by the retention time of the main peak. Any peak with an RRT<1 elutes before the main peak, and any peak with an RRT>1 elutes after the main peak.

For purposes of the present invention, "substantially free of impurities" shall be understood to include bendamustine-containing compositions in which the amount of total impurities is less than about 5%, as calculated on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after a period of about 15 months at a temperature of from about 5° C. to about 25° C. The amount of impurities is further calculated as being based upon the original amount bendamustine (or salt thereof) being present in the composition or formulation.

For purposes of the present invention, a pharmaceutically acceptable fluid is a fluid which is suitable for pharmaceutical use.

Preferably, the amount of any individual degradant in the inventive compositions does not exceed 2% PAR as determined by HPLC at a wavelength of 223 nm after storage periods of at least about 15 months at a temperature of from about 5° C. to about 25° C. In some aspects, the amount of time the inventive compositions demonstrate long term storage stability is at least about 18 months and preferably at least about 2 years when stored under the conditions described herein.

In accordance with one aspect of the invention there are provided long term storage stable bendamustine-containing compositions including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including

i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant.

The total impurities in the inventive compositions resulting from the degradation of the bendamustine in the compositions is less than about 5% PAR as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of from about 5° C. to about 25° C., and thus have long term stability for at least the same period of time or longer. Preferably, the bendamustine-containing compositions demonstrate long term storage stability for at least about 2 years, especially when stored at the lower (refrigerated) temperatures. In one embodiment, the amount of total impurities in the inventive compositions resulting from the degradation of the bendamustine is less than about 3% PAR as determined by HPLC at a wavelength of 223 nm after at least about 2 years at a temperature of from about 5° C. to about 25° C.

In some aspects of the invention, the bendamustine concentration in the inventive compositions is from about 10 mg/mL to about 100 mg/mL, preferably 20 mg/mL to about 60 mg/mL. Preferably the bendamustine concentration in the inventive compositions is from about 25 mg/mL to about 50 mg/mL, and more preferably from about 30 mg/mL to about 50 mg/mL. It will be understood that compositions containing any useful concentration within the ranges, i.e. 10, 20, 25, 30, 35, 40, 45, 50, 55, 60 . . . 100 are contemplated. In other embodiments, the bendamustine concentration in the composition is about 50 mg/mL. In alternative aspects, the amount of bendamustine is outside these ranges but the amounts will be sufficient for single or multiple administrations of dosages generally regarded as effective amounts.

In several embodiments of the invention, pharmaceutically acceptable fluid is non-aqueous and may be, but is not necessarily, a solvent for the bendamustine or salt thereof. Within this aspect, the pharmaceutically acceptable fluid is propylene glycol (PG) or polyethylene glycol (PEG). In other embodiments of the invention however, the pharmaceutically acceptable fluid is a mixture of PEG and PG. For example, the pharmaceutically acceptable fluid can include about 50% PEG and about 50% PG. Alternatively, pharmaceutically acceptable fluid includes about 95% PEG and about 5% PG. The amount of PEG and PG can also be varied within the ranges, i.e. the ratio of PEG:PG in the pharmaceutically acceptable fluid can range from about 95:5 to about 50:50. Within this range, is a pharmaceutically acceptable fluid containing about 75% PEG and about 25% PG, and preferably 80% PEG and 20% PG. In another embodiment, a pharmaceutically acceptable fluid can include about 85% PEG and about 15% PG while another preferred pharmaceutically acceptable fluid includes about 90% PEG and about 10% PG. The molecular weight of the PEG will be within the range of pharmaceutically acceptable weights although PEG 400 is preferred in many aspects of the invention.

Without meaning to be bound by any theory or hypothesis, the hydroxide of the polyethylene glycol molecule is less reactive than the hydroxides of propylene glycol. As a result, the ester forms at a slower rate in polyethylene glycol than propylene glycol and the resulting bendamustine degradants are unexpectedly and substantially reduced over extended periods of time when PEG is a substantial part of the pharmaceutically acceptable fluid.

The bendamustine-containing compositions according to several preferred aspects of the invention include a stabilizing amount of an antioxidant. For purposes of the present invention, "stabilizing amount" shall be understood to include those amounts which increase or enhance the stability of the bendamustine in the compositions described herein. The presence of one or more antioxidants described herein thus contributes, at least in part to the long term stability of the composition. Within this guideline, suitable antioxidant concentrations in the compositions can range from about 2.5 mg/mL to about 35 mg/mL, and preferably from about 5 mg/mL to about 20 mg/mL or from about 10 mg/mL to about 15 mg/mL. In some other embodiments, the concentration of the antioxidant in the bendamustine-containing composition is about 5 mg/mL.

Suitable antioxidants for inclusion include those which are pharmaceutically acceptable for use in human and veterinary formulations although not limited to those currently regarded as safe by any regulatory authority. For example, the antioxidant can be selected from among lipoic acid, thioglycerol (also known as monothioglycerol) and analogs thereof, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds, dihydrolipoic acid and mixtures of the foregoing. Preferably, the antioxidant is thioglycerol, lipoic acid or a mixture thereof. Some particularly preferred embodiments of the invention include thioglycerol.

In view of the foregoing, some preferred long term storage stable bendamustine-containing compositions in accordance with the invention compositions include:

I. a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including

i) polyethylene glycol and propylene glycol; and

ii) a stabilizing amount of thioglycerol; or

II. a) about 50 mg/mL bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including

i) about 90% PEG and about 10% PG; and

ii) about 2.5 mg/mL thioglycerol.

Each of these compositions have the same stability profiles already described, i.e. having less than about 5% total impurities, PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

In accordance with other aspects of the invention, there are provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof;

b) a pharmaceutically acceptable fluid including one or more of the following: PG, ethanol, PEG, benzyl alcohol and glycofurol; and

c) a stabilizing amount of a chloride salt.

These compositions also have the low levels of impurities and long term stability mentioned herein. Preferred pharmaceutically acceptable fluids include PG, PEG or ethanol in this embodiment of the invention. Preferably, the PEG is PEG 400. If desired, glycerin and/or 88% (w/w) lactic acid can be added to the pharmaceutically acceptable fluid.

Suitable chloride salts include but are not limited to organic chloride salts, sodium chloride, choline chloride, hydrochloride salts of amino acids and mixtures thereof. Thus, as will be appreciated by those of ordinary skill, one can select from among a number of suitable chloride salts and it is Applicants' intention that the scope of the invention includes all such chloride salts that are capable of being included in bendamustine-containing formulations for

extended periods without having a deleterious effect on the drug. In one embodiment of the invention, the chloride salt concentration is from about 10 to about 300 mg/mL. In another embodiment, the chloride salt concentration is from about 50 to about 215 mg/mL. In one preferred embodiment, the chloride salt concentration is about 215 mg/mL.

In accordance with another aspect of the invention, there is provided long term storage stable bendamustine-containing compositions, including:

a) bendamustine or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable fluid including DMSO.

These compositions also have the low levels of impurities and long term stability mentioned herein. In some aspects, the bendamustine concentration in these compositions is from about 10 mg/mL to about 100 mg/mL. Preferably, the bendamustine concentration is from about 20 mg/mL to about 50 mg/mL, more preferably from about 25 mg/mL to about 50 mg/mL. In an alternative embodiment, the bendamustine concentration is about 50 mg/mL.

Another embodiment of the invention provides methods of treating cancer in mammals. The methods include administering to a mammal in need thereof an effective amount of one of the bendamustine-containing compositions described herein. Since the active ingredient portion of the inventive composition is an FDA-approved drug, those of ordinary skill will recognize that the doses of bendamustine employed in this aspect of the invention will be similar to those employed in any treatment regimens designed for bendamustine as marketed under the trade name TREANDA. The patient package insert containing dosing information is incorporated herein by reference. The methods of treatment also include administering the inventive formulations for any purpose or physical condition for which bendamustine has been indicated as being useful.

Another embodiment of the invention includes methods of preparing bendamustine-containing compositions described herein. The methods include reconstituting lyophilized bendamustine in a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, benzyl alcohol and glycofurol; and

ii) a stabilizing amount of a chloride salt; or

C) DMSO.

The steps are carried out under pharmaceutically acceptable conditions for sterility and manufacturing.

In a further aspect of the invention, there are provided methods of controlling or preventing the formation of impurities in bendamustine-containing compositions during long term storage. The methods include combining an amount of bendamustine or a pharmaceutically acceptable salt thereof with a sufficient amount of a pharmaceutically acceptable fluid containing one of the following:

A) i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and

ii) a stabilizing amount of a chloride salt; or

C) DMSO.

Further optional steps in accordance therewith include transferring one or more pharmaceutically acceptable doses of the formulations into a suitable sealable container and storing the sealed container at a temperature of from about 5° C. to about 25° C. As a result of carrying out these steps, it is possible to control or substantially prevent the formation of impurities which otherwise occur with bendamustine-containing compositions during long term storage so that the artisan is provided with bendamustine-containing formulations having less than about 5% total impurities PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

The compositions of the present invention can be packaged in any suitable sterile vial or container fit for the sterile storage of a pharmaceutical such as bendamustine. Suitable containers can be glass vials, polypropylene or polyethylene vials or other special purpose containers and be of a size sufficient to hold one or more doses of bendamustine.

A further aspect of the invention includes kits containing lyophilized bendamustine or a pharmaceutically acceptable salt thereof in a first container or vial; and, in a second container, a sufficient amount of a pharmaceutically acceptable fluid such as those described herein, i.e. one of the following:

A) i) PEG, PG or mixtures thereof; and

ii) a stabilizing amount of an antioxidant;

B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and

ii) a stabilizing amount of a chloride salt; or

C) DMSO.

For purposes of this embodiment, the amount of fluid which is sufficient is an amount which allows the bendamustine to be dissolved or dispersed to a degree which renders the liquid composition ready for use.

As will be appreciated by those of ordinary skill, the kit will contain other pharmaceutically necessary materials for storing and/or administering the drug, including instructions for storage and use, additional diluents, if desired, etc.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in one of ethanol, propylene glycol and benzyl alcohol as indicated in Table 1 below. 215 mg/ml of choline chloride was added in half of the samples as a source of soluble chloride ions. The samples were maintained at 40° C. and analyzed periodically for drug content and total impurities. The results obtained are presented in Table 1.

TABLE 1

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
BDM - 10 mg/mL		Initial	10.43	0.27
Choline chloride -	40° C.	48 hrs	10.48	1.27
215 mg/mL		7 day	10.26	2.11
Ethanol qs to 1 mL				
BDM - 10 mg/mL		Initial	10.55	0.27
Ethanol qs to 1 mL	40° C.	48 hrs	10.30	2.39
		7 day	9.55	6.66
BDM - 10 mg/mL		Initial	9.99	0.21
Choline chloride -	40° C.	48 hrs	9.95	0.60
215 mg/ml		7 day	9.43	2.31
Propylene glycol qs				

TABLE 1-continued

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
to 1 mL				
BDM - 10 mg/mL		Initial	9.68	0.21
Propylene glycol qs	40° C.	48 hrs	9.45	0.88
to 1 mL		7 day	9.00	3.44
BDM - 10 mg/mL		Initial	9.95	1.19
Choline Chloride -	40° C.	48 hrs	9.89	3.51
215 mg/mL		7 day	8.97	4.24
Benzyl alcohol qs to 1 mL				
BDM - 10 mg/mL		Initial	9.52	0.33
Benzyl alcohol qs	40° C.	48 hrs	8.67	4.18
to 1 mL		7 day	7.49	7.84

Note:
In Table 1 the total % impurities include total contributions from peaks at various RRTs.

As shown in Table 1, the bendamustine formulations are very stable in solutions containing solvent and chloride salt. Table 1 shows that bendamustine, when dissolved at a concentration of about 10 mg/mL, in a pharmaceutically acceptable fluid, such as ethanol and propylene glycol, and containing a stabilizing amount of a chloride salt, such as choline chloride, had less than about 5% after at least 7 days storage at 40° C.

The data presented in Table 1 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of a chloride salt having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including ethanol alone exhibited more than 6.5 total degradants after 7 days storage at 40° C. The sample including benzyl alcohol alone exhibited more than 7.5% total degradants after 7 days storage at 40° C. Bendamustine-containing compositions with such high levels of degradation would not be suitable for long-term storage.

Example 2

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in DMSO. The samples were maintained at 40° C. and analyzed periodically for drug content and impurity profile. The results obtained are presented in Table 2.

TABLE 2

Stability of Bendamustine HCl in DMSO

Formulation	Temp	Time	Content (mg/mL)	% Total Imp
BDM - 10 mg/mL		Initial	10.2	0.23
DMSO qs to 1 mL	40° C.	48 hrs	9.80	0.30
		1 week	10.0	0.56

Note:
In Table 2 the total % impurities include total contributions from peaks at various RRTs.

Table 2 shows that bendamustine, when dissolved in DMSO, had substantially no increase in total degradants. The data presented in Table 2 translates to bendamustine-containing compositions including DMSO having a shelf life of at least about 15 months at 5° C. and 25° C. In fact, such compositions are expected to have long term stability for periods beyond 15 months, i.e. up to 2 years or greater.

Example 3

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 20 mg/ml in polyethylene glycol 400 and 5 mg/ml of lipoic acid was added as a stabilizing antioxidant as indicated in Table 3 below. The samples were maintained at 40° C. or 25° C. and analyzed after 15 days for drug content and impurities. The results obtained are presented in Table 3.

TABLE 3

Stability of Bendamustine (20 mg/ml) in PEG 400 and Antioxidants

Antioxidant	T ° C.	Time days	% Initial	% Imp RRT 0.58	% Total Imps
None	25	15	97.6	2.08	2.28
	40	15	56.3	2.17	41.9
Lipoic Acid	25	15	98.5	<LD	0.23
5 mg/ml	40	15	97.5	0.33	0.53

<LD = Below Level of Detection

As shown in Table 3, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as polyethylene glycol, in the presence of a stabilizing amount of an antioxidant, such as lipoic acid, had substantially no increase in total degradants after a period of 15 days. The data presented in Table 3 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of an antioxidant having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including PEG alone, on the other hand, which did not contain an antioxidant, did not exhibit stabilizing effects at 40° C. This sample had more than 40% more total impurities than the sample including lipoic acid. Bendamustine-containing compositions with such high levels of total impurities would not be suitable for long-term storage.

Example 4

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 5 mg/ml of thioglycerol, α-lipoic acid or dihydrolipoic acid was added as a stabilizing antioxidant as indicated in Table 4 below. The samples were maintained at 40° C. and analyzed after 15 days or one month for drug content and impurity profile as indicated in Table 4 below. The results obtained are presented in Table 4.

TABLE 4

Stability of Bendamustine (50 mg/ml) in 90% PEG 400, 10% Propylene Glycol and Antioxidant

					% Impurities RRT		%
Antioxidant	T (° C.)	Time	Content (mg/mL)	% Initial	HP1 0.59	PG ester 1.10	Total Imps
Thioglycerol	40	initial	48.8	100	<LD	<LD	0
	40	1 month	48.5	99.4	0.06	0.20	0.71
α-lipoic acid	40	initial	49	100	<LD	<LD	0
	40	15 days	48.8	99.6	0.19	0.13	0.32
	40	1 month	48.7	99.4	0.34	0.26	0.79
Dihydrolipoic acid	40	initial	49.3	100	<LD	<LD	0
	40	1 month	47.7	97.4	0.63	0.12	1.84

<LD = Below Level of Detection

As shown in Table 4, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as a combination of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of an antioxidant, such as thioglycerol, α-lipoic acid or dihydrolipoic acid, had substantially no increase in total degradants after a period of 1 month. This data supports the position that bendamustine-containing compositions according to the invention have a shelf life of at least about 2 years when stored at temperatures between 5° C. and 25° C.

Example 5

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in a mixture of polyethylene glycol 400 and propylene glycol as indicated in Table 5 below. 5 mg/ml of lipoic acid was added as a stabilizing antioxidant. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed after 1 week, 15 days or one month for drug content and impurity profile as indicated in Table 5 below. The results obtained are presented in Table 5.

TABLE 5

Stability of Bendamustine (50 mg/ml) and Lipoic Acid (5 mg/ml) in PEG400 and Propylene glycol

					% Area of degradants			%
Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	HP1 0.58	PG ester 1.10	PG ester 1.13	Total Imp.
BDM -	Initial		49.6	100	BDL	BDL	BDL	0.18
50 mg/mL	40° C.	1 W	49.0	98.8	0.05	0.13	BDL	0.38
Lipoic acid-		15 d	48.3	97.4	0.08	0.26	BDL	0.55
5 mg/mL		1 M	48.0	96.8	0.11	0.43	0.13	1.03
PEG	25° C.	15 d	49.6	100.0	BDL	0.10	BDL	0.30
400:PG	5° C.	1 M	48.4	97.6	0.05	0.19	BDL	0.43
(75:25) qs		1 M	49.6	100.0	BDL	0.07	BDL	0.27
to 1 mL								
BDM-	Initial		50.2	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	49.9	99.4	BDL	0.15	BDL	0.30
Lipoic acid-		15 d	49.1	97.8	0.06	0.35	BDL	0.73
5 mg/mL		1 M	49.0	97.6	0.09	0.90	0.25	1.82
PEG	25° C.	15 d	49.9	99.4	BDL	0.12	BDL	0.32
400:PG		1 M	49.7	99.0	BDL	0.25	BDL	0.59
(50:50) qs								
to 1 mL	5° C.	1 M	50.0	99.6	BDL	0.11	BDL	0.33
BDM-	Initial		50.8	100	BDL	BDL	BDL	0.21
50 mg/mL	40° C.	1 W	50.4	99.2	BDL	0.11	BDL	0.30
Lipoic acid-		15 d	49.7	97.8	0.07	0.17	BDL	0.43
5 mg/mL		1 M	49.7	97.8	0.13	0.27	0.09	0.84
PEG	25° C.	15 d	50.8	100.0	BDL	0.10	BDL	0.26
400:PG		1 M	50.8	100.0	0.05	0.14	BDL	0.39
(90:10) qs	5° C.	1 M	50.8	100.0	BDL	0.06	BDL	0.34
to 1 mL								

BDL = Below Detectable Limit

As shown in Table 5, bendamustine, when dissolved in certain mixtures of polyethylene glycol and propylene glycol and a stabilizing amount of lipoic acid, had substantially no increase in total degradants after a period of 1 month. The data presented in Table 5 translates to bendamustine-containing compositions having a shelf life of at least about 2 years when stored at temperatures between 5° C. and at 25° C.

Example 6

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol and α-lipoic acid was added as a stabilizing antioxidant as indicated in Table 6 below. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed for drug content and impurity profile as indicated in Table 6 below. The results obtained are presented in Table 6.

TABLE 6

Stability of Bendamustine in 90% PEG 400, 10% PG and α-lipoic acid

Formulation	Temp	Time Per.	Amt. mg/ml	% of Initial	% Area of degradants 0.59	1.10	1.13	1.15	1.17	1.20	1.22	1.30	% Total Imp.
BDM-	Initial		51.0	100	0.20	0.06	<LD	<LD	<LD	<LD	<LD	LD	0.26
50 mg/mL	40° C.	1 M	50.5	99.0	0.21	0.31	0.13	0.07	0.13	0.10	<LD	<LD	0.95
α-lipoic		2 M	49.7	97.5	0.22	0.71	0.28	0.14	0.12	0.21	0.12	<LD	2.02
acid-		3 M	48.7	95.5	0.22	1.01	0.45	0.21	0.14	0.37	0.16	0.05	2.96
10 mg/mL	25° C.	3 M	50.5	99.0	0.20	0.36	0.07	<LD	<LD	0.10	<LD	<LD	0.73
PEG		6 M	50.4	98.8	0.22	0.60	0.17	0.06	0.06	0.09	0.10	0.08	1.44
400:PG	5° C.	6 M	50.9	99.8	0.16	0.05	<LD	<LD	<LD	<LD	<LD	<LD	0.21
(90:10) qs		12 M	50.6	99.2	0.20	0.18	<LD	<LD	<LD	<LD	<LD	<LD	0.38
to 1 mL	Initial		50.3	100	0.18	<LD	<LD	<LD	<LD	<LD	<LD	<LD	0.18
BDM-	40° C.	1 M	50.0	99.4	0.19	0.32	0.08	0.06	0.08	0.06	0.06	<LD	0.85
50 mg/mL		2 M	49.8	99.0	0.19	0.65	0.21	0.12	0.13	0.23	0.14	0.06	1.85
α-lipoic		3 M	49.5	98.4	0.15	0.89	0.37	0.17	0.13	0.32	0.10	<LD	2.40
acid-		6 M	47.0	93.4	0.20	1.76	0.66	0.19	0.31	0.47	0.33	0.17	4.93
15 mg/mL	25° C.	3 M	50.0	99.4	0.20	0.35	0.08	<LD	<LD	<LD	0.11	<LD	0.79
PEG		6 M	49.5	98.4	0.19	0.58	0.15	0.06	0.07	0.09	0.08	0.10	1.38
400:PG	5° C.	6 M	50.3	100	0.17	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.23
(90:10) qs		12 M	50.2	99.8	0.19	0.15	<LD	<LD	<LD	<LD	<LD	<LD	0.34
to 1 mL													

<LD = Below Level of Detection

The data reported in Table 6 along with the data in Table 5 demonstrates that bendamustine solutions are stable when dissolved in mixtures of PEG and PG and 5-15 mg/mL α-lipoic acid. As shown in Table 6, bendamustine, when dissolved in combinations of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of lipoic acid, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6-12 months at 5° C. and 25° C. The data corresponds to bendamustine solutions being stable under ambient or refrigerated storage conditions for well in excess of 2 years, and thus long term stable.

Example 7

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 2.5 mg/ml of thioglycerol was added as an antioxidizing agent. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 7 below. The results obtained are presented in Table 7.

The stability is similar to that of α-lipoic acid samples in Example 6 above. As shown in Table 7, bendamustine, when dissolved in a combination of polyethylene glycol and propylene glycol, and a stabilizing amount of thioglycerol, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6 months at 25° C. The data reported supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for about 2 years.

Example 8

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 85% PEG 400 and 15% PG in the presence of 5 mg/ml of thioglycerol. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 8 below. The results obtained are presented in Table 8.

TABLE 7

Stability of Bendamustine in 90% PEG 400, 10% PG and Thioglycerol

Formulation	Temp	Time Per.	Amt mg/ml	% of Initial	RRTs of degradants 0.15	0.37	1.10	1.13	1.15	1.17	1.18	1.20	1.22	% Total Imp.
BDM -	Initial		50.3	100	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	0.00
50 mg/mL	40° C.	15 d	50.2	99.8	BDL	BDL	0.18	BDL	BDL	BDL	0.05	0.08	BDL	0.31
Thio		1 M	49.9	99.2	BDL	0.12	0.32	0.07	BDL	BDL	0.09	0.08	BDL	0.75
glycerol-		2 M	49.1	97.6	BDL	0.18	0.56	0.24	0.09	0.17	0.19	0.12	0.11	1.76
2.5 mg/mL		3 M	48.8	97.0	BDL	0.23	0.85	0.34	0.16	0.30	0.34	0.29	0.19	2.94
PEG	25° C.	3 M	49.9	99.2	0.06	0.12	0.23	0.07	BDL	0.06	0.07	0.06	BDL	0.67
400:PG		6 M	49.3	98.0	BDL	0.23	0.53	0.22	0.11	BDL	0.21	0.22	0.20	2.07
(90:10) qs														
to 1 mL														

BDL = Below Detectable Limit

TABLE 8

Stability of Bendamustine in 85% PEG 400, 15% PG and Thioglycerol

Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	% Total Imp.
BDM - 50 mg/mL	Initial		51.5	100	0.12
Thioglycerol - 5 mg/mL	40° C.	1 M	50.4	97.9	1.18
PEG 400:PG (85:15)	25° C.	1 M	51.4	99.8	0.41
qs to 1 mL		3 M	50.4	97.9	1.21
	5° C.	3 M	51.0	99.0	0.26

The stability is similar to that of thioglycerol samples in Example 7 above. As reported in Table 8, total impurities did not exceed 2% at 40° C. or 25° C. storage over one month, or at 25° C. and 5° C. storage after three months. The data reported in Table 8 supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for at least about 2 years if not longer.

We claim:

1. A sterile container containing a liquid bendamustine-containing composition comprising

bendamustine, or a pharmaceutically acceptable salt thereof, wherein the bendamustine concentration in the composition is about 25 mg/ml;

a pharmaceutically acceptable fluid consisting of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol; and

a stabilizing amount of an antioxidant,

wherein the total impurities resulting from the degradation of the bendamustine is less than about 5% peak area response, as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of about 5° C. to about 25° C.

2. The sterile container of claim **1**, wherein the antioxidant is monothioglycerol.

3. The sterile container of claim **1**, wherein the antioxidant is monothioglycerol in a concentration of about 5 mg/mL.

4. The sterile container of claim **1**, wherein the composition is stable for at least about 15 months at 5° C. or for at least about 15 months at 25° C.

5. The sterile container of claim **1**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and one or more of propylene glycol, ethanol, benzyl alcohol, and glycofurol.

6. The sterile container of claim **1**, wherein the liquid bendamustine-containing composition comprises about 100 mg of bendamustine, or a pharmaceutically acceptable salt thereof.

7. The sterile container of claim **1**, wherein the liquid bendamustine-containing composition comprises about 100 mg of bendamustine.

8. A liquid bendamustine-containing composition comprising

bendamustine, or a pharmaceutically acceptable salt thereof, and a stabilizing amount of an antioxidant, in a pharmaceutically acceptable fluid;

wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol; and

wherein the bendamustine concentration in the pharmaceutically acceptable fluid is about 25 mg/mL,

wherein the total impurities resulting from the degradation of the bendamustine is less than about 5% peak area response, as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of about 5° C. to about 25° C.

9. The composition of claim **8**, wherein the antioxidant is monothioglycerol.

10. The composition of claim **8**, wherein the antioxidant is monothioglycerol in a concentration of about 5 mg/mL.

11. The composition of claim **8**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and one or more of propylene glycol, ethanol, benzyl alcohol, and glycofurol.

12. The composition of claim **8**, wherein the bendamustine concentration in the composition is 25 mg/mL.

13. The sterile container of claim **5**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol.

14. The sterile container of claim **5**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and propylene glycol.

15. The sterile container of claim **5**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and ethanol.

16. The sterile container of claim **5**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and benzyl alcohol.

17. The sterile container of claim **5**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and glycofurol.

18. The composition of claim **11**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol.

19. The composition of claim **11**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and propylene glycol.

20. The composition of claim **11**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and ethanol.

21. The composition of claim **11**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and benzyl alcohol.

22. The composition of claim **11**, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and glycofurol.

* * * * *